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Hypoglycemic Coma With Ketoacidosis in Nondiabetic Alcoholics

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Five nondiabetic, chronically alcoholic patients presented in a comatose state during a two month prospective study and were found to be ketoacidotic. All of the patients were men, 28 to 59 years old. The usual history was one of chronic heavy, daily alcohol consumption until one to three days before presentation, when persistent anorexia, abdominal distress, nausea and vomiting commenced, with abstention from food thereafter. The patients were found to be in hypoglycemic coma, with diaphoresis, tachypnea and tachycardia, and immediately awoke when intravenous infusion of glucose was started. Serum glucose ranged between 19 and 27 mg per dl, the average arterial pH was 7.19 and the mean anion gap was 25 mEq per liter. Reaction with Acetest tablets was positive for ketones in both serum and urine in three of the patients. Serum β-hydroxybutyrate was elevated in the four patients in whom it was measured. Lactic acidosis was not present.

All patients were managed with prolonged intravenous infusions of glucose and saline solutions, and within 12 to 18 hours they were feeling well and findings on serum chemistry studies were normal. Follow-up after three months showed no repeated difficulties. The combination of alcoholic ketoacidosis and hypoglycemic coma in nondiabetic persons has not been described in the literature as a clinical entity; it may, however, represent a common but unrecognized syndrome. Therefore, because of its potentially serious consequences and because treatment is simple and effective, this entity must be thought of in alcoholic patients with altered mental status.

HYPOGLYCEMIA induced by alcohol was first described by Brown and Harvey[1] in 1941 in six chronic alcoholic persons, but was felt for the next two decades to be secondary to congeners in alcoholic beverages. There have since been relatively few reported cases of alcohol-induced hypoglycemia—probably a significant underestimate of the incidence of this entity in chronic alcoholism.[2] Alcoholic ketoacidosis was first described by Dillon and associates[3] in 1940, but has only recently been further documented and investigated.[4-7] There are relatively few reports of this entity in the literature, but its occurrence may not be infrequent in cases of chronic alcoholism. With the exception of one report, more than three

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fourths of the reported cases have occurred in women; as a result, hormonal mechanisms have been proposed.[6]

The combination of alcohol-induced hypoglycemic coma occurring concomitantly with ketoacidosis, however, has not yet been described as a clinical entity, although a few such cases can be found included in previously published series.[4-7] We report five cases of hypoglycemic coma with ketoacidosis in nondiabetic alcoholic men. The clinical and laboratory findings, as well as possible causes and mechanisms, are described. This entity, we feel, is both important and not uncommon in cases of chronic alcoholism.

Methods

Each of the five patients presented to the Johns Hopkins Hospital emergency department and was seen by one of the authors (E.V.P.) over the space of two months, one a winter month (December) and the other a summer month (June). Except for one patient who was admitted to hospital, each remained in the emergency department less than 24 hours before leaving—either by discharge or against medical advice. All of the patients returned for follow-up evaluation. Blood chemistry, hematologic and arterial blood gas studies were done using routine hospital procedures. Arterial lactic acid levels were measured by a Dupont Automatic Clinical Analyzer, using the method of Marbach and Weil,[8] modified by Varley.[9] Serum β-hydroxybutyrate levels were measured using the principles outlined by Antonis and associates.[10] Serum insulin determinations were done using the radioimmunoassay technique of Morgan and Lazaran.[11] A *toxicology screen* (routine for all comatose patients in the emergency department) was done in each case; it includes qualitative urine and blood assays for the detection of alcohol, methanol, barbiturates, phenytoin, salicylate, glutethimide, meprobamate, chlordiazepoxide, diazepam, methaqualone, xanthines, phenothiazines, tricyclic antidepressants, opium alkaloids, synthetic narcotics, propoxyphene and amphetamines. Semiquantitative ketone determinations were done with Acetest tablets (Ames).

Reports of Cases

CASE 1. A 39-year-old man was brought to the emergency department one morning in a stuporous, semicomatose state, having been found at home in that state by a friend. He had been a regular, heavy drinker of alcohol for 22 years, but stopped drinking two to three days before because of lack of funds. He had not eaten for several days because of mild epigastric pain, nausea and vomiting. The patient later said he had not been exposed to toxins or taken drugs. There was no personal or family history of diabetes. The history was otherwise unremarkable.

On physical examination the patient had rapid, labored breathing and tachycardia. He was moderately diaphoretic with hepatomegaly and was minimally responsive to maximal verbal or pain stimulus. A study of blood using Dextrostix showed a low glucose level; therefore, thiamine was given intravenously, followed by 100 grams of glucose as a 50 percent dextrose solution. The patient immediately became alert and fully oriented and was able to give a coherent history, stating that the last thing he remembered was retiring to bed the previous night. The serum glucose level was 25 mg per dl and laboratory findings (Table 1) showed metabolic acidosis with weakly reactive Acetest test for ketones in serum; serum β-hydroxybutyrate was found to be greatly elevated (9.8 mEq per liter). Toxicology screen was negative. Glucose and saline solution was given intravenously, and within 12 hours arterial pH and blood chemistry values were normal, and the patient was discharged.

On follow-up at one month and three month intervals, continued alcohol ingestion was noted but no episodes similar to the earlier one had occurred. A glucose tolerance test was carried out and gave normal findings.

CASE 2. A 43-year-old man with a known history of chronic alcoholism was brought to the emergency room early one afternoon because he had lain in bed since morning in an unarousable state. He had stopped his usual daily intake of one quart of whiskey a day several days before, and had since then stopped eating regularly because of troublesome nausea and vomiting. There was no history of diabetes, nor any recent ingestion of toxins or drugs. The family history was negative for diabetes.

On physical examination the patient was comatose and afebrile, there were Kussmaul-type respirations and tachycardia, and blood pressure was minimally elevated. He was diaphoretic, with no acetone smell on his breath, and there was a grade II/VI systolic murmur and moderate hepatomegaly. He responded slightly to maximum noxious stimuli. Hypoglycemia was shown to be

present by Dextrostix. He was given 100 grams of glucose as 50 percent solution and awoke almost immediately, becoming fully alert and communicative. Results of laboratory studies are shown in Table 1 and included a glucose value of 21 mg per dl, with arterial pH of 7.18 and weakly reactive Acetest test for ketones in serum. Serum insulin was later found to be appropriately low, at 3 μU per ml. Dextrose and saline solution was given intravenously for 18 hours, and the patient left the hospital. Serum chemistry values and pH were normal.

On follow-up clinic visits in one month and three months the patient admitted to continuous alcohol ingestion, but denied any similar episodes. A glucose tolerance test was done and showed normal values except for a minimally elevated two hour value.

CASE 3. A 31-year-old man with a ten-year history of heavy alcohol abuse and idiopathic seizure disorder for which he took phenytoin, 300 mg per day, was brought in by his girl friend in a comatose state. He had stopped drinking alcohol approximately two days before. Since then, he had eaten and drunk little because of some anorexia, nausea and vomiting. His girl friend reported that he had a single grand mal seizure the previous night, but awoke and later retired to bed in a fully alert state. He had not taken any drugs or toxins, except for a marijuana cigarette three days before, and had discontinued taking his phenytoin at about the same time he stopped drinking. There was no personal or family history of diabetes, and the history was otherwise unremarkable.

On physical examination, the patient was tachypneic and tachycardiac with mild diaphoresis; findings included minimal facial flushing, slight hepatomegaly, and a stuporous state from which he was minimally arousable by maximal pain stimuli. A low blood glucose level was shown by Dextrostix, and he became fully alert and communicative after 100 grams of dextrose in 50 percent solution was infused intravenously. The blood glucose level was later found to be 27 mg per dl; other laboratory values are shown in Table 1. Treated with glucose and saline given intravenously, he was discharged in 12 hours, after serum chemistry values and arterial pH returned to normal, and he was eating regularly.

A follow-up clinic visit two months later showed that the patient had had no further similar

TABLE 1.—*Laboratory Summary of Nondiabetic Alcoholic Patients With Hypoglycemic Ketoacidotic Coma*

Case	Arterial pH	Serum Acetest for Ketones	Urine Acetest for Ketones	Serum Glucose (mg/dl)		Serum Bicarbonate (mEq/liter) (normal 24-30)		Lactic Acid, Arterial (mEq per liter) (normal .5-1.5)	Serum β-hydroxybutyrate (mEq per liter) (normal<.05)	Anion Gap ($Na+K-[Cl+HCO_3]$)	Serum Bilirubin (mg/dl)	Serum Insulin (μU/ml)	SGOT (IU/liter) (normal<17)	SGPT (IU/liter) (normal<17)	Amylase (Caraway U) (normal<160)
				Initial	Discharge	Initial	Discharge								
1	7.16	+	+	25	105	14	21	2.6	9.8	27	1.0	..	55	54	98
2	7.18	+	+	21	120	15	20	2.3	..	21	0.8	3	40	50	120
3	7.23	−	−	27	125	17	24	..	7.3	22	0.7	..	35	29	80
4	7.19	−	−	21	110	13	22	2.2	8.5	29	1.1	5	30	26	65
5	7.18	+	+	19	105	15	23	2.4	5.9	24	0.9	2	31	67	90
MEAN	7.19	..	..	23	..	15	..	2.4	7.9	25	0.9	3	38	45	91

episodes, but that he consumed alcohol regularly. A glucose tolerance test gave normal findings, as did liver function tests, except for a mildly elevated serum glutamic oxaloacetic transaminase value.

CASE 4. A 28-year-old man with a history of chronic alcoholism and alcohol withdrawal seizures was brought in by police after being found unresponsive in an alley, apparently having lain there for a number of hours. He later related that he had stopped drinking alcohol one or two days before, and that he had since been having epigastric pains with anorexia, nausea and vomiting. He had spent the night in the alley because of the warm weather, he claimed. He denied any toxin or drug ingestion, and said there was no personal or family history of diabetes. When he entered the emergency room, he was diaphoretic, with Kussmaul-type respirations and tachycardia.

On physicial examination the abdomen was normal and there was no hepatomegaly. The patient was comatose, barely responsive to painful physical stimuli. Dextrostix showed low serum glucose, and thiamine and 100 grams of dextrose were immediately given intravenously. He awoke quickly thereafter, alert and oriented. On laboratory studies, the blood glucose level was 21 mg per dl and the arterial pH was 7.19; other findings are shown in Table 1. A saline and dextrose solution was administered intravenously for 18 hours, at which time pH and electrolyte values had returned to normal. Because of persistent nausea, a prochlorperazine rectal suppository was administered, after which adequate oral intake of foods and liquids was restored.

On follow-up visit in six weeks it was found that the patient had continued drinking alcohol but had had no further similar episodes. An oral glucose tolerance test was done and results were within normal limits.

CASE 5. A 59-year-old man was brought by relatives to the emergency department one morning in a comatose state after he was found to be unresponsive at home. He had a 35-year history of heavy alcohol abuse, averaging half a pint of whiskey a day. He had stopped eating and drinking the previous morning, however, because of some epigastric pain with persistent nausea and vomiting. The patient later said there had been no toxin or drug exposure, nor any personal or family history of diabetes. The history was remarkable for an incompletely documented episode in 1973 when he presented to the emergency department in a comatose state with decorticate posturing. He was found at the time to be severely hypoglycemic, and regained consciousness upon the infusion of a concentrated dextrose solution. He was then admitted to hospital, where there was no recurrence of symptoms. A five-hour glucose tolerance test was carried out and showed no abnormalities. Percutaneous liver biopsy was also done and showed fatty changes.

On physical examination, the patient was diaphoretic, with a temperature of 35°C (95°F) rectally, tachycardia and rapid, labored breathing. He had moderate hepatomegaly, and responded only to deep painful stimuli with withdrawal motions. Dextrostix showed a low glucose level, so he was given thiamine intravenously, followed by 100 grams of glucose as a 50 percent solution. He awoke quickly thereafter, and was able to give a coherent history. Blood glucose level was reported to be 19 mg per dl and other laboratory findings (Table 1) showed metabolic acidosis with moderately reactive Acetest reaction in both serum and urine. Blood alcohol was undetectable, and the serum insulin value was low (2 μU per ml). He was admitted to hospital and treatment began with a continuous intravenous infusion of a glucose and saline solution, without bicarbonate. By late evening, body temperature, arterial pH and serum chemistry values were normal. The following day a five-hour glucose tolerance test was done and showed no abnormalities. The next morning an adrenocorticotropic hormone stimulation test was done and findings were normal. Later in the morning the patient asked to go home and was discharged in good condition. Follow-up in the medical clinic two months later indicated that no further similar episodes had occurred.

Results

All patients had a history of significant chronic alcohol intake, and generally were young, the average age being 40 years. The patients were all men, and all had a period of abstinence from alcohol for an average of two days immediately preceding their presentation in the hospital emergency department. This abstinence was usually related to the symptoms of anorexia, epigastric pain, nausea and vomiting. None of the patients had a personal or family history of diabetes, or

any renal, chronic lung or liver disease, nor was there any recent ingestion of drugs or toxins.

Each had gone to sleep the previous night, and was found to be in an unarousable state the next day upon presentation to the emergency department. The characteristics of the coma in each case were typical of hypoglycemic coma, with diaphoresis, tachypnea and tachycardia in all, and Kussmaul-type breathing noted in two patients. None of the patients was febrile, and one was hypothermic. Four of the five patients had evidence of hepatomegaly on physical examination. Bowel sounds were normal in all patients, without evidence of ileus. None appeared grossly hypovolemic on physical examination.

Admission laboratory data included low serum glucose values for every patient, verified by subsequent autoanalyzer values of less than 30 mg per dl in each case. Metabolic acidosis was present in every patient, with an average arterial pH of 7.19 and serum bicarbonate value of 14.8 mEq per liter. The average anion gap—serum Na + K − (serum Cl + serum HCO_3)—was 25 mEq per liter. Acetest examination of undiluted serum and urine was positive in three of the patients. In four of the five patients, including both patients with negative Acetest serum and urine reactions, serum β-hydroxybutyrate levels were notably elevated, with a mean value of 8.9 mEq per liter. Lactic acidosis did not appear to be present; arterial lactate was only mildly elevated in the four patients in whom it was measured. A toxicology screen of blood, urine and emesis specimens was done in each case and was negative in each. There was no evidence of hyperinsulinism, as serum insulin was appropriately low during hypoglycemia in each of the three patients in whom it was measured.

Despite the presence of abdominal pain, there was no evidence of pancreatitis in any of the patients: serum amylase was within normal limits in all patients. Serum bilirubin was normal in all five patients, although both serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels were somewhat elevated in all patients, averaging 38 and 45 units, respectively.

All patients were managed in a similar manner —first given a rapid bolus of a 50 percent dextrose solution, followed by prolonged intravenous infusion of approximately 3 liters of a saline and 5 percent dextrose solution over 12 to 18 hours while still in the emergency department. Coma in all cases responded rapidly to initial infusion of dextrose concentrates. Thereafter, the patients were observed closely and continued to do well with the glucose and saline infusions alone. Sodium bicarbonate was not used in any of the patients. One patient was given prochlorperazine because of nausea. At the time of discharge all patients had normal serum glucose levels and serum bicarbonate values were greater than 20 mEq per liter. They were all able to tolerate food and liquid without difficulty upon discharge. Each patient, along with any accompanying relative or friend, was told of the importance of continued and regular eating, and was instructed to return if difficulties with eating developed.

All patients did well after discharge with no recurrence of symptoms, although four of the patients admitted continued alcohol ingestion. A follow-up glucose tolerance test was carried out in each case and findings were normal.

Discussion

Although originally described in 1940 by Dillon,[3] only more recently has the entity of alcoholic ketoacidosis been further documented and investigated, primarily by Jenkins and associates[4] in 1971 and Levy and co-workers[5] in 1973. In the latter report, six episodes were described of metabolic acidosis in five nondiabetic, chronically alcoholic patients, each of whom had a history of protracted vomiting and abstention from food for several days. One of the patients presented in an unconscious state, and all were found to be significantly acidotic, with an average arterial pH of 7.16, ranging from 6.96 to 7.29, with anion gaps of 15 to 34 mEq per liter. Two patients died, one with aspiration pneumonia and the other with cardiac arrest. Only this latter patient was found to be hypoglycemic; all others were noted to have normal or elevated serum glucose levels. Similarly, in the reported cases of alcoholic ketoacidosis described by Jenkins and co-workers,[4] Cooperman and associates[6] and Fulop and associates,[12] all but two patients were noted to have normal or elevated serum glucose levels. In contrast, our patients with alcoholic ketoacidosis presented in profound hypoglycemic coma, responsive in each case to concentrated glucose solutions given intravenously.

Heretofore, a striking preponderance in the literature of women with alcoholic ketoacidosis—15 of 19 cases—has been noted by Cooperman,[6]

although this was not true in the cases reported by Fulop and co-workers.[12] On the other hand, the combination of alcoholic hypoglycemic coma and ketoacidosis seems to occur most often in men. The patients were similar, however, in other respects—most of them having had a heavy alcohol intake up until one to three days before presentation, at which time drinking and food consumption were stopped, usually because of nausea, vomiting and epigastric distress. There was no history of toxin or drug ingestion, nor was there any evidence of diabetes mellitus found on later glucose tolerance testing. Each of the patients went to sleep the previous night and was found to be unarousable the next day upon presentation to the emergency department. Finally, hypothermia, which was a common feature in Harvey's series,[1] was present in only one of our five patients.

Both the metabolic acidosis and hypoglycemia in each of our patients were corrected within 12 to 18 hours with intravenous administration of glucose and saline, as has been reported by others in the literature.[4-6,11] Thiamine was given intravenously before glucose infusion in most cases in order to prevent possible precipitation of Wernicke disease. Recovery was complete without the introduction of alkali. Antiemetics were used in one case for symptomatic relief of nausea, so that oral intake could be reestablished. Four of the five patients were managed as outpatients in the emergency department and were discharged directly from there, rather than being admitted to hospital. One of the patients, who was also hypothermic, was admitted to hospital, but his body temperature, pH and serum chemistry values had returned to normal within 12 hours. At the time of clinic follow-up, none of the patients reported any continued difficulties, though a number had later recommenced their alcohol intake.

It is of note that in two of our patients Acetest reactions were not positive for ketones in either serum or urine, despite clear-cut acidosis in both of them. Serum lactic acid was measured in one of these two patients and was normal. The most likely explanation for this observation is the relative insensitivity of the nitroprusside reagent to acetone and especially β-hydroxybutyrate.[13] In fact, β-hydroxybutyrate levels were substantially elevated in both of these patients, and indeed in all four patients in whom this measurement was made. As has been shown by Levy and colleagues[5] and Cooperman and associates,[6] ketone bodies in alcoholic ketoacidosis are mainly in the form of β-hydroxybutyrate, with relatively low levels of acetoacetate, probably because of the high NADH/NAD ratio (nicotinamide adenine dinucleotide [reduced form]/nicotinamide adenine dinucleotide). Hence, the Acetest reaction may show little or no reactivity despite the presence of ketoacids, as in our series and others.[5,6,12] If this is not kept in mind, it can lead to underestimation of the degree of ketosis or failure to recognize it.

The precise mechanism and cause of the alcoholic hypoglycemia, as well as the ketoacidosis, remain uncertain. It is also unknown why some patients become hyperglycemic and ketoacidotic. Cooperman[6] suggested that hormonal—ovarian and placental—mechanisms might be playing a role, since most of the reported cases of alcoholic ketoacidosis occurred in women. This appears unlikely, however, in that both Fulop's series[12] and our own show a predominance of men. The factors contributing to the hypoglycemia are probably numerous. First, patients have typically not eaten for a number of hours to days, depleting available hepatic glycogen stores. Second, hepatic gluconeogenesis has been suppressed by prior ethanol intake. This suppression of gluconeogenesis, in turn, is thought to result from the pronounced increase in the NADH/NAD ratio generated during ethanol metabolism. This elevated level of NADH can persist for an abnormally long period in the livers of alcoholics.[14] Finally, it has been suggested that decreased levels of circulating alanine may account for the diminished gluconeogenesis in the presence of ethanol.[15,16]

While fasting, the precursors of hepatic gluconeogenesis include amino acids, lactate and glycerol. Amino acids enter this pathway by conversion either to pyruvate or, via the tricarboxylic acid cycle, to oxaloacetate, and thence to phosphoenolpyruvate. A high NADH/NAD ratio, however, is an effective suppressant of the tricarboxylic acid cycle. Lactate, which has been noted to be slightly elevated in some patients—and in two of the four patients in our series in whom it was measured—must be oxidized to pyruvate in order to enter the gluconeogenic pathway. This oxidation is inhibited by the high NADH/NAD ratio, however, and the reduction of pyruvate to lactate is favored, with potentially significant accumulation of the latter.

The mechanism of the coexisting ketoacidosis in our patients is perhaps equally obscure. During the prolonged fasting there is increased fat mobi-

lization peripherally, with a resultant increased fat load upon the liver. In very large amounts, alcohol can itself produce peripheral fat mobilization. Cortisol and growth hormone levels have been found to be elevated in patients with alcoholic ketoacidosis by Levy and co-workers,[5] and may represent another important factor in the increased lipolytic rate. In the liver, oxidation of these increased amounts of free fatty acids is carried out by the NAD-requiring Krebs cycle. As discussed above, this is impeded because of the altered redox state from ethanol metabolism, resulting in the production of ketones and ketoacidosis. Substantial ultrastructural changes have been noted in the hepatic mitochondria of alcoholics,[17] and it may be that hepatic ketone production is further enhanced by favoring the rate of fatty acyl entry into the mitochondria, controlled by the enzyme, fatty acyl carnitine transferase,[18] and by loosening of hepatic mitochondrial respiratory control, as suggested by Cooperman.[6] The defect and ketosis are rapidly reversed by the intravenous infusion of glucose.

The fact that five cases of hypoglycemic coma with ketoacidosis were observed in nondiabetic alcoholic patients in the course of two months in a large city emergency room, suggests that this syndrome is probably not uncommon among the chronic alcoholics seen in emergency departments of large hospitals. During this time, three additional alcoholic patients with a similar history of recent food and alcohol abstinence were seen in the emergency department with complaints of mild abdominal pain, nausea and vomiting, and were found to be in nondiabetic ketoacidosis, but were normoglycemic. To give some perspective, 15 cases of diabetic ketoacidosis were seen in the emergency department by the same observers during this same period. Perhaps less severe degrees of this metabolic imbalance masquerade as acute alcohol intoxication, and may be unrecognized in busy emergency departments, particularly when a patient is asleep on a stretcher for several hours during which an intravenous dextrose solution with the usual vitamin supplements is being given—which is routine. This group of patients undoubtedly will recover. However, yet another, less fortunate group of patients who also may have simply appeared to be intoxicated may be sent home without intravenously given glucose or even a meal. Therefore, particularly because of the easily reversible nature of hypoglycemia and alcoholic ketoacidosis, and because of their potentially serious outcome if left untreated, these entities must enter prominently in the differential diagnosis of alcoholic patients with altered mental status.

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